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(D) analyzing the interaction of all or part of each of said potential amino acids side chains from said group with all or part of the remainder of said protein backbone structure to generate a set of optimized proteins sequences.

31. (Currently Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions; of a desired target protein, said protein structure comprising:

i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and

ii) a plurality of variable residue positions;

(B) altering at least one supersecondary structure parameter value of said protein backbone structure prior to establishing a group of potential amino acids;

(C) classifying each variable residue position as either a core, surface or boundary residue;

(D) establishing a group of potential amino acids side chains for each of said variable residue positions, wherein a first group for a first variable position has a first set of at least two amino acid side chains, and wherein a second group for a second variable position has a second set of at least two different amino acid side chains, and wherein said sets are different; and

(E) analyzing the interaction of all or part of each of said amino acids side chains from said group with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences.

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COO<sup>+</sup>.
- 32. (Canceled Herein) - New Claim 61
  - 33. (Canceled Herein) - New Claim 63
  - 34. (Canceled Herein) - New Claim 64
  - 35. (Canceled Herein) - New Claim 65
  - 36. (Canceled Herein) - New Claim 66
  - 37. (Canceled Herein) - New Claim 67
  - 38. (Canceled Herein) - New Claim 68
  - 39. (Canceled Herein) - New Claim 69
  - 40. (Canceled Herein) - New Claim 71
  - 41. (Canceled Herein) - New Claim 72
  - 42. (Canceled Herein) - New Claim 73
  - 43. (Canceled Herein) - New Claim 74
  - 44. (Canceled Herein) - New Claim 75
  - 45. (Canceled Herein) - New Claim 76
  - 46. (Canceled Herein) - New Claim 77
  - 47. (Canceled Herein)
  - 48. (Canceled Herein)
  - 49. (Canceled Herein)
  - 50. (Canceled Herein)

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51. (Previously Canceled)

52. (Previously Canceled)

53. (Currently Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) ~~receiving a protein backbone structure with variable residue positions; of a desired target protein, said protein structure comprising:~~

i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and

ii) a plurality of variable residue positions;

(B) altering at least one supersecondary structure parameter value of said protein backbone structure prior to establishing a group of potential amino acids side chains;

(C) establishing a group of potential amino acids side chains for each of said variable residue positions, wherein a first group for a first variable position has a first set of at least two amino acid side chains, and ~~wherein a second group for a second variable position has a second set of at least two different amino acid side chains;~~ and

(D) analyzing the interaction of all or part of each of said amino acids side chains from said group with all or part of ~~the remainder~~ of said protein backbone structure to generate a set of optimized protein sequences.

54. (Canceled Herein)

55. (Canceled Herein)

56. (Currently Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) ~~receiving a protein backbone structure with variable residue positions; of a desired target protein, said protein structure comprising:~~

i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and

ii) a plurality of variable residue positions;

(B) altering at least one supersecondary structure parameter value of the protein backbone structure of said protein;

(C) establishing a group of potential ~~retamers~~ amino acid side chains for a plurality of variable residue positions of said protein, wherein at least one of said ~~retamers~~ amino acid side chains is from a hydrophilic amino acid; and

(D) analyzing the interaction of all or part of each of said potential amino acid side chains from said group with all or part of said protein structure to generate a set of optimized proteins sequences, wherein said analyzing step includes the use of at least one scoring function.

57. (Currently Amended) A method according to claim 56 wherein said ~~first and second sets of retamers~~ amino acid side chains are different.

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58. (Currently Amended) A method according to claim 56 wherein said ~~first and second sets of rotamers~~ amino acid side chains are the same.

59. (Original) A method according to claim 56 wherein said hydrophilic amino acid is selected from the group consisting of serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine, and histidine.

60. (Original) A method according to claims 53-59 further comprising physically generating at least one member of said set of optimized protein sequences and experimentally testing said sequence for a desired function.

61. (New) A method according to claim 30, 31, or 53 wherein said analyzing step comprises a DEE computation.

62. (New) A method according to claim 56 wherein said analyzing step further comprises a DEE computation.

63. (New) A method according to claim 56 wherein said set of optimized protein sequences comprises the globally optimal protein sequence.

64. (New) A method according to claim 61 or 62 wherein said DEE computation is selected from the group consisting of original DEE and Goldstein DEE.

65. (New) A method according to claim 30, 31, or 53 wherein said analyzing step includes the use of at least one scoring function.

66. (New) A method according to claim 56 or 65 wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

67. (New) A method according to claim 65 wherein said analyzing step includes the use of at least two scoring functions.

68. (New) A method according to claim 65 wherein said analyzing step includes the use of at least three scoring functions.

69. (New) A method according to claim 65 wherein said analyzing step includes the use of at least four scoring functions.

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70. (New) A method according to claim 66 wherein said scoring function is an atomic solvation scoring function.
71. (New) A method according to claim 70 wherein said atomic solvation scoring function includes a scaling factor that compensates for over-counting.
72. (New) A method according to claim 30, 31, 53, or 56 further comprising experimentally testing at least one member of said set.
73. (New) A method according to claim 63 further comprising the step of:  
generating a list of additional optimal sequences from said globally optimal protein sequence.
74. (New) A method according to claim 73 wherein said generating includes the use of a Monte Carlo search.
75. (New) method according to claim 30, 31, 53, or 56 wherein said analyzing step comprises a Monte Carlo computation.
76. (New) A method according to claim 75 further comprising the step of:  
testing some or all of said protein sequences from said list to produce potential energy test results.
77. (New) A method according to claim 76 further comprising the step of:  
analyzing the correspondence between said potential energy test results and theoretical potential energy data.
78. (New) A method according to claim 30, 31, 53, or 56 further comprising modulating the protein backbone structure.
79. (New) A method according to claim 30, 31, 53, or 56 wherein said variable residue positions comprise one or more non-core positions.
80. (New) A method according to 53 wherein step (c) comprises a second group for a second variable position has a second set of at least two amino acid side chains.
81. (New) A method according to claim 80 wherein said first and second amino acid side chains are different.
82. (New) A method according to claim 80 wherein said first and second amino acid side chains are the same.
83. (New) A method according to 30, 31, 53 or 56, wherein said at least one non-variable residues is fixed.

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84. (New) A method according to claim 30, 31, 53 or 56, wherein said at least one non-variable residue is floated.

85. (New) A method according to claim 30, 31, 53 or 56 wherein said variable residue positions are structurally functional residue positions.

86. (New) A method according to claim 30, 31, 53, or 56 wherein said variable residue positions are biologically functional residue positions.

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